Since there is no evidence or practical reason of record that would have led the skilled artisan to the claims, Applicants submit that the claims are patentably distinct.

Details of Applicants' Arguments

By the above amendments, Applicants have overcome the 35 USC 112, second paragraph rejections. By the following arguments, Applicants traverse the 35 USC 103 rejection because of lack of prima facie obviousness. The basis for the rejection is apparently reflected by the Examiner's statement in Paper #7. The Examiner states that Claims 1-8 and 13, 21 under 35 USC 103(a) stand rejected on the grounds that:

> "It is notoriously well accepted in the art that a natural viral infection will create the best immune response and thereby provide the best protection against re-infection by the same virus. Based on the teachings of Rodriguez et al., it would have been prima facie obvious to one of ordinary skill in the art to produce a peptide based vaccine to those portions of the virus that are recognized by the natural infection because the immune system responds to them in providing protection. Based on the teachings of Zamorano et al., one of ordinary skill in the art would have an expectation of success in eliciting an immune response to peptides."

Without addressing the truth of the above statement, Applicants, nonetheless, traverse the rejection because the general knowledge that "a natural viral infection will create the best immune response and thereby provide the best protection against re-infection by the same virus" would not have led Rodriguez et al to the claimed polypeptide vaccines. Differently put, the general knowledge does not inform on how to modify the Rodriguez et al in order to produce the claimed vaccine.

Applicants hasten to note that in the instance of FMDV, infected animals can become persistent carriers of FMDV for several years and thus may become a source of new outbreaks. See cited Lubroth et al, column 1, second paragraph.

ISSUES

The fundamental issue here is whether there is an error in determining the difference between the prior art and the claims.

It is well established that in determining obviousness, one must make a finding as to the scope and content of the prior art to which the invention pertains,

the difference between the prior art and the claims, and the level of ordinary skill in the art.

Apparently, the difference between the prior art and the claims as perceived by the Examiner is stated at page 3 of Paper #7 as follows: "[T]he motivation to produce a peptide based vaccine to the non-structural proteins of FMDC comes from the difference between the heat killed vaccine and the natural infection."

To the contrary, Applicants submit that the difference resides in the failure of the prior art to teach vaccines comprising non-structural polypeptides. Read for what it stands, Rodriguez et al relates to the use of structural and non-structural peptides for diagnostics for FMDV. The closest Rodriguez et al gets to vaccines is the disclosure of an oil emulsion commercial vaccine (Laboratorios Sobrino, Olot, Spain) which included ethlyenimine inactivated virus (equivalent to 5 times 10^7 p.f.u.) from each of strains of serotype C (C-S*), A (A5 Fra 1/68) and O (O-Granollers Sp/71). Beyond this vaccine, Rodriguez et al does not disclose other vaccines, let alone the claimed vaccines. At the risk of being rhetorical, it would appear that with the non-structural polypeptides at hand for use as diagnostics, Rodriguez et al would have used them as FMDV, vaccines had it been successful in making said vaccines.

Lacking in Rodriguez et al is any teaching or suggestion of how to formulate the polypeptides into a vaccine. This shortcoming is not cured by the proposition that a natural infection provides the best protection. There is no basis in this knowledge or Rodriguez et al that would have provided to the skilled artisan how to modify the prior art in order to arrive at the claimed vaccine, with a reasonable expectation of success.

Negating a reasonable expectation of success is evidence and practical reason of record relating to problems associated with making FMDV vaccines and problems with natural infection. The practical problems encountered in making FMDV vaccines, pointed out the cited U.S. Patent 4,605,512 are instructive. At col. 1, lines 55 to col. 2, line 6, the patent states that:

> "Production of FMDV whole virus vaccine is beset by several major difficulties. First, because of the infectious character of the virus, laboratory growth of virus for vaccines must be done in isolated facilities under high containment. Second, the virus based vaccines

often display an unacceptable variation in potency after production and inactivation, Third, the vaccines must be tested under very controlled conditions to insure proper efficiency of attenuation or inactivation. Otherwise, the vaccine may cause accidental active infection or subacute progressive disease in treated animals. All of these production problems result in higher costs for the ultimate vaccine. In addition to the above described production problems, the use of whole virus vaccines results in a small, but a significant, number of allergic side reactions in the treated animals. These undesirable side effects are probably caused by the many irrelevant antigenic determinants of the viral and non-viral proteins that usually contaminate viral vaccines."

Also, see page 3, lines 1-16 of the specification stating some the associated problems as follows:

"Three things in particular, have to be taken into account in the development of vaccines having specific epitopes:

1. Polymorphism of proteins of the pathogen occurs especially in the protein sections involved in the immune response. RNA viruses especially ("quasi-species", contain regions of extremely high sequence variability.

2. Especially in the case of the T-cell immune response, there is a high variability of single individuals of the host species. As a rule, a T-helper cell recognizes a specific antigenic peptide only in combination with a MHC-II molecule (Schwartz, 1985). Each individual expresses its own set of MHC molecules, which are encoded by having high alleilic variation (MHC polymorphism). A T-cell response to peptides can, therefore, be individually different.

3. The T-cell fractions exhibit very heterogeneous effector mechanisms which, nevertheless, as a rule, correlate with MHC restriction (Mosmann et al., 1989). For FMDV in cattle, it was hitherto only possible to demonstrate MHC_II-restricted T- helper functions (Glass et al., 1989; Glass et., 1990; Glass et al., 1992; Collen et al., 1991).

Given these problems, one would be hard pressed to argue that diagnostics containing structural and/or non-structural proteins suggest the claimed vaccines -

the making of which is fraught with problems. If that were the case, the vaccine art would have developed a vaccine for AIDS. Unfortunately, it is not.

"Zamorano et al. teach that structural peptide-based vaccines can elicit B- and T-cell immune responses. The peptides in the reference are 10 amino acids in length and they correspond to amino acids residues of the VP1 structural protein sequences of FMDV. Zamorano et al. also teach the peptides in the test vaccines can be used with or without a coupled protein carrier."

Lacking from Samoan et al. is any teaching or suggestion of how to make vaccines based on non-structural polypeptides.

Morgan et al teaches protection of cattle and swine against FMDV using biosynthetic peptide vaccines comprising a virus protein 1 (VP1) peptide (structural protein) expressed in E. Coli as a fusion protein with 190 amino acids (AA) of the LE' protein of the tryptophan of E. Coli.

Lacking from Morgan et al is any teaching or suggestion of how to make vaccines based on non-structural polypeptides.

Given the afore-stated problems associated with making FMDV vaccines, one would be hard pressed to argue that diagnostics or vaccines relating to structural proteins suggest vaccines relating to non-structural proteins. In view of the foregoing amendments and discussions, Applicants submit that the claims are patentably distinct over the prior art and the Examiner is justified in allowing them

Respectfully submitted,

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